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INPLASY

Efficacy, Safety, and Strategy-Modifying Factors of Pulsed Field Ablation for Persistent and Long-Standing Persistent Atrial Fibrillation: a protocol for a systematic review and meta-analysis

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Zhou, LW; Xie, JH.

Corresponding author:
Yuanlin Zhou

18780032305@163.com

Author Affiliation:
West China School of Medicine,Sichuan University, Sichuan University affiliated Chengdu Second People's Hospital,Chengdu Second People's Hospital.

ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 24 April 2026 and was last updated on 24 April 2026.

INTRODUCTION

Review question / Objective This review aims to evaluate the efficacy, safety, and strategy-modifying factors of pulsed field ablation (PFA) in adults with persistent atrial fibrillation (PerAF) and long-standing persistent atrial fibrillation (LSPAF). Specifically, the review addresses:
(1) the overall rhythm and safety outcomes of PFA in PerAF/LSPAF;
(2) the comparative effectiveness and safety of PFA versus cryoballoon ablation and other non-PFA strategies in head-to-head studies; and
(3) whether different lesion-set tiers, including PVI-only, PVI plus posterior wall isolation/ablation, and beyond-pulmonary-vein or extensive substrate-modification strategies, are associated with different outcomes.

Rationale Persistent and long-standing persistent atrial fibrillation represent more advanced forms of AF with greater substrate complexity, and the role of pulsed field ablation in these populations remains incompletely defined. Existing reviews have mainly pooled mixed AF populations and have not adequately addressed the heterogeneity of lesion sets, comparator strategies, endpoint definitions, and antiarrhythmic drug handling in PerAF/LSPAF studies. A focused systematic review and meta-analysis is therefore warranted to synthesize the available evidence on the efficacy, safety, and strategy-modifying factors of PFA in this specific population.

Condition being studied Persistent atrial fibrillation and long-standing persistent atrial fibrillation. This review focuses on the use of pulsed field ablation in these more substrate-complex AF populations, in which lesion-set selection, antiarrhythmic drug handling, blanking-period definitions, and comparator heterogeneity may materially affect interpretation of efficacy and safety outcomes.

METHODS

Search strategy Searches combined three concept blocks using database-specific syntax:
(A) pulsed field ablation / electroporation terms;
(B) atrial fibrillation terms;
(C) persistent, long-standing persistent, or non-paroxysmal disease terms.
Representative terms included "pulsed field ablation", "pulse field ablation", "pulsed-field ablation", "irreversible electroporation", "electroporation", "Farapulse", "FARAWAVE", "pentaspline", "atrial fibrillation", "persistent", "long-standing persistent", "non-paroxysmal", "PerAF", and "LSPAF". Full database-specific search strategies were prepared in the supplementary appendix.

Participant or population Adult patients with persistent atrial fibrillation or long-standing persistent atrial fibrillation who underwent pulsed field ablation. Studies enrolling mixed AF populations were eligible only if persistent-specific or long-standing persistent-specific data were extractable.

Intervention Pulsed field ablation strategies for PerAF/LSPAF, including but not limited to:
PVI-only;
PVI plus posterior wall isolation (PWI), left atrial posterior wall isolation (LAPWI), or posterior wall ablation (PWA);
beyond-pulmonary-vein or extensive substrate-modification strategies;
and electrogram-guided PFA approaches.

Comparator For comparative studies, eligible comparators included cryoballoon ablation, radiofrequency ablation, hybrid-convergent ablation, or alternative within-PFA strategies (for example, electrogram-guided PFA versus anatomical PVI plus PWI).
For exploratory single-arm syntheses, no external comparator was required.

Study designs to be included Prospective or retrospective comparative cohort studies, prospective single-arm trials, registries, and single-arm cohort studies reporting efficacy and/or safety outcomes of PFA in PerAF/LSPAF.Case reports, physiology-only companion reports, workflow-only or acute safety-only reports without clinically interpretable follow-up outcomes, and studies without extractable persistent-specific data for the target population were excluded.Randomized controlled trials and non-randomized comparative studies (prospective or retrospective cohort studies and other comparative observational designs).

Eligibility criteria Studies were eligible if they:
(1) enrolled adults with PerAF or LSPAF;
(2) evaluated PFA-based ablation;
(3) reported interpretable efficacy and/or safety outcomes; and
(4) for direct comparative meta-analysis, provided extractable paired binary data.
If studies reported both off-AAD and on-AAD rhythm outcomes, off-AAD data were preferred. If AAD status was not separated, the study-level primary rhythm endpoint was retained and explicitly marked as AAD-unseparated. Composite effectiveness endpoints that incorporated AAD escalation were retained for descriptive synthesis only and were not entered into the exact-count exploratory single-arm pooling.
Full-text exclusions included companion/physiology reports, mixed AF without extractable persistent-specific raw outcomes, acute registry/workflow/safety-focused reports, ineligible mixed populations, short-term or mid-term follow-up only, and very small special-case series.

Information sources The following databases were searched from inception to 18 April 2026: PubMed, Web of Science, Embase, Cochrane Library, and Scopus. In addition, reference lists of included studies and relevant review articles were screened manually to identify additional eligible reports.

Main outcome(s) The main efficacy outcome was atrial arrhythmia recurrence after the blanking period at approximately 12 months of follow-up, or a study-level equivalent rhythm endpoint judged clinically comparable. When both off-AAD and on-AAD outcomes were reported, off-AAD outcomes were preferred.
For direct comparative efficacy analyses, the effect measure was risk ratio (RR) with 95% confidence intervals.

Additional outcome(s) Additional outcomes included major complications and, for exploratory strategy-based syntheses, pooled 12-month event-free proportions and pooled major-complication proportions within predefined lesion-set tiers.
Major complications were extracted as reported by the original studies and then mapped, where possible, to a clinically meaningful framework broadly consistent with contemporary HRS/EHRA/ECAS-style definitions, including events requiring invasive management or escalation of care, prolonging hospitalization, causing major

hemodynamic compromise, stroke/systemic embolism, myocardial infarction, clinically significant tamponade, major vascular complications requiring intervention or transfusion, or causing persistent disability or death.

Data management Title/abstract screening, full-text assessment, and data extraction were performed independently by two reviewers, with disagreements resolved through discussion. Extracted information included study design, population characteristics, lesion set, comparator type, follow-up, blanking period, antiarrhythmic drug handling, efficacy endpoints, and safety endpoints.

Quality assessment / Risk of bias analysis Comparative cohort studies were assessed using the Newcastle–Ottawa Scale (NOS). Single-arm studies and registries were evaluated using a predefined modified 7-point tool covering cohort representativeness, population clarity, strategy definition, endpoint clarity, follow-up adequacy, safety reporting, and completeness/attrition. Quality scores were used to contextualize interpretability and risk of bias rather than to weight pooled estimates directly.

Strategy of data synthesis Direct comparative efficacy outcomes were synthesized using pairwise meta-analysis in Review Manager 5.4, with risk ratios (RRs) and 95% confidence intervals.
For rare safety events, especially major complications, risk difference (RD) with 95% confidence intervals was used in order to retain double-zero-event comparative studies.
Exploratory single-arm syntheses were conducted in R (version 4.5.0) using the metaprop function in the meta package, with logit transformation, inverse-variance weighting, DerSimonian–Laird random-effects modeling, and a continuity correction of 0.5.
Studies without harmonizable exact counts were synthesized narratively. Formal publication-bias assessment was not performed for the main comparative analyses because too few studies were available.

Subgroup analysis Planned subgrouping and stratified interpretation included:
(1) comparator type, particularly cryoballoon ablation versus other non-PFA comparators;
(2) lesion-set tier, including PVI-only, PVI plus PWI/LAPWI/PWA, and beyond-PV/extensive substrate-modification strategies;
(3) efficacy versus safety outcomes;
and (4) within-PFA strategy contrasts when only single-study evidence was available, such as electrogram-guided versus anatomical PFA.
When comparator heterogeneity was judged clinically fundamental, subgroup-specific results were presented without an across-subgroup pooled estimate.

Sensitivity analysis Sensitivity analyses were planned and displayed to test the robustness of recurrence and safety findings when clinically relevant but methodologically less harmonized studies were incorporated into expanded evidence displays. In the completed review, supplementary sensitivity displays were generated for safety and recurrence, including analyses involving Hirokami 2025, Turagam 2024, and Gunawardene 2023. These sensitivity displays were interpreted as robustness checks rather than as primary pooled estimates for the main-text conclusions.

Language restriction No explicit language restriction was prespecified in the search strategy; studies had to provide sufficient information for eligibility assessment and data extraction.No language restriction.

Country(ies) involved China.

Other relevant information This review was not prospectively registered. At the time of INPLASY submission, the literature search, study selection, data extraction, quality assessment, and data synthesis had already been completed, and the review was completed but not yet published. This registration is therefore retrospective and is intended to improve transparency and reduce unnecessary duplication. The registration reflects the methods actually used in the completed review.

Keywords Pulsed field ablation; persistent atrial fibrillation; long-standing persistent atrial fibrillation; posterior wall isolation; systematic review; meta-analysis.

Dissemination plans The results of this systematic review and meta-analysis will be submitted to a peer-reviewed journal in the field of cardiology/electrophysiology. Supplementary materials, including the search strategies, PRISMA checklist, study-characteristics tables, and figure set, will accompany the manuscript as appropriate. Data and code availability statements will be completed in accordance with target-journal.

Contributions of each author
Author 1 - Yuanlin Zhou.

Email: 18780032305@163.com
Author 2 - Jianhua Xie.
Email: xieianhua@163.com